this amendment is proper since it places the claims in better form for appeal, reduces issues for appeal, does not raise any new issues, and does not require further consideration or search.

Rejection Under 35 U.S.C. § 112, first paragraph

Claims 11-13 and 19-22 were rejected under 35 U.S.C. § 112, first paragraph, as not being enabled. Applicants respectfully traverse this rejection.

The Legal Standard

The Court of Appeals for the Federal Circuit (CAFC) has described the legal standard for enablement under § 112, first paragraph, as whether one skilled in the art could make and use the claimed invention from the disclosures in the patent coupled with information known in the art without undue experimentation (*See, e.g.*, Genentech, Inc. v. Novo Nordisk A/S, 108 F3d at 165, 42 USPQ2d at 1004 (quoting In re Wright, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); See also In re Fisher, 427 F.2d at 839, 166 USPQ at 24; United States v. Telectronics, Inc., 857 F.2d 778 (Fed. Cir. 1988); In re Stephens, 529 F.2d 1343 (CCPA 1976)). The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation (M.I.T. v. A.B. Fortia, 774 F.2d 1104 (Fed. Cir. 1985)). In addition, as affirmed by the Court in Spectra-Physics, Inc. v. Coherent, Inc., 827 F.2d 1524 (Fed. Cir. 1987), a patent need not teach, and preferably omits, what is well known in the art.

Whether making or using the invention would have required undue experimentation, and thus whether the disclosure is enabling, is a legal conclusion based upon several underlying factual inquiries. See In re Wands, 858 F.2d 731, 735, 736-737, 8 USPQ2d 1400, 1402, 1404

(Fed. Cir. 1988). As set forth in Wands, the factors to be considered in determining whether a claimed invention is enabled throughout its scope without undue experimentation include the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, and the breadth of the claims. In cases that involve unpredictable factors, "the scope of the enablement obviously varies inversely with the degree of unpredictability of the factors involved." In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The fact that some experimentation is necessary does not preclude enablement; what is required is that the amount of experimentation 'must not be unduly extensive.' Atlas Powder Co., v. E.I. DuPont De Nemours & Co., 750 F.2d 1569, 1576, 224 USPQ 409, 413 (Fed. Cir. 1984).

The test is not merely quantitative, since a considerable amount of experiment is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the invention claimed.

Ex parte Jackson, 217 USPQ 804, 807 (1982)

As stated in the MANUAL OF PATENT EXAMINING PROCEDURE §2164.04 (7th ed. 1998), *citing* In re Wright, 999 F.2d 1557, 1562 (Fed. Cir. 1993), the examiner has the initial burden to establish a reasonable basis to question the enablement of the application.

A specification disclosure which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining

the subject matter sought to be patented **must be taken as being in compliance with the enablement requirement** of 35 U.S.C. § 112, first paragraph, unless there is a reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support.

Id. at § 2164.05 (emphasis added).

The patent examiner cannot just assert that the application is not enabled. As stated in In re Marzocchi at 439 F.2d 220 (CCPA 1971:

[I]t is incumbent upon the Patent Office, whenever a rejection on this basis is made [, enablement under § 112, first paragraph], to explain *why* it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. Otherwise, there would be no need for the Appellant to go to the trouble and expense of supporting his presumptively accurate disclosure.

Id. at 224.

The MPEP instructs examiners to make specific findings of *facts* to rebut Appellants' presumption and "specifically identify what information is missing and why one of skill in the art could not supply the information without undue experimentation." MPEP at § 2164.05. The examiner should provide references to support a *prima facie* case of lack of enablement. *Id.*

Applicants Provide an Enabling Disclosure of the Claimed Subject Matter

The specification describes in profound detail the methods to enable one of skill in the art to obtain "an isolated nucleic acid molecule encoding a scavenger receptor protein" and *Applicants have shown actual reduction to practice of this.* The general methods are disclosed on page 10, lines 2-20 of the specification. Methods to use cDNA as a nucleic acid probe are detailed on page 25, lines 10-20, methods to generate a genomic library are disclosed on page 34 and 35; screening patient samples is described on page 40, lines 6-16; hybridization methods are described on pages 40 and 41. It is even disclosed on page 38 , lines 12-20 that the cDNA can be used to construct probes to screen libraries for other receptors including human equivalents.

The cDNA represents the portion of the genomic DNA, without the introns, that encodes the protein. By possessing the cDNA, one is enabled to obtain the corresponding genomic clone. Methods are described in detail to accomplish this. Furthermore, by possessing the hamster clone, one is enabled to obtain the mouse and human clones using methods described in the disclosure, and known in the art. *Applicants have demonstrated constructive reduction to practice* of the genomic DNA for SR-BI, *and* the genomic DNA for SR-BI from different species.

The enclosed declaration under 37 C.F.R. 1.132 clearly describes methods known in the art at the time of filing that would enable one of skill in the art to produce an isolated genomic nucleic acid encoding a scavenger receptor protein. The cDNA for the hamster SR-BI sequence is disclosed and encodes for a scavenger receptor protein. This cDNA can be used as a probe for isolating homologues in different species as described in the enclosed declaration. The disclosure of the cDNA sequence enables one of skill in the art to isolate homologues from other

species. Furthermore, in a recent decision by the CAFC, the court ruled that in the event that the specification described and enabled various possible species and provided specific information on methods of use, description of one species would enable one of ordinary skill to practice the method pertaining to the genus. *Amgen Inc. v. Hoescht Marion Roussel, Inc.* 01-1191, -1218 - (C.A.F.C.)

The Applicants demonstrate in the declaration under 37 C.F.R. 1.132, and submitting lab notebook pages that the hamster SR-BI cDNA could be used to make a probe to screen a mouse genomic library and isolate the mouse SR-BI homologue with routine experimentation. By this same methods, SR-BI homologues could be found from *any* species. There was no reason to also do this for human also because Calvo et al had been published by this time (1994) and the Applicants knew that the CLA-1 of Calvo was the human homologue of SR-BI. Cloning the human SR-BI homologue was predicted to be the same as the sequence in the database submitted by Calvo et al. This demonstrates that the disclosure filed in 1994 was in fact enabling for "an isolated nucleic acid encoding a scavenger receptor protein". One of skill in the art was able to make and use the claimed invention from the disclosures in the patent coupled with information known in the art without undue experimentation. The legal standard has been met.

Claim 19 was rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor had possession of the claimed invention. Applicants respectfully traverse this rejection.

It was recently clarified in Enzo Biochem that the written description requirement "may be satisfied if in the knowledge of the art the disclosed function is sufficiently correlated to a particular, known structure. See *Enzo Biochem*, 296 F.3d at 1324, 63 USPQ2d at 1613. Although it has been previously expected that all candidates of a genus be described in detail, a recent decision by the C.A.F.C., stated that "the specification's description of producing the claimed EPO in two species of vertebrate or mammalian cells adequately supports claims covering EPO made using the genus vertebrate or mammalian cells, [and] renders Eli Lilly listless in this case." *Amgen*, 126 F.Supp2d at 149, 57 USPQ2d at 1507. The C.A.F.C. has ruled that adequate description of one species satisfies the written description for the corresponding genus of compounds.

Claim 19 is directed to an isolated nucleic acid molecule that encodes a human scavenger receptor protein. The hamster cDNA sequence encoding a scavenger receptor protein is disclosed in the specification along with a description to use the hamster sequence to isolate the genus of scavenger receptor homologues. It is explicitly described on page 38, lines 13-20 of the specification that the cDNA sequence can be used as a probe to screen other genomic libraries from different species. The example of human is given. One of skill in the art would be aware of methods to screen genomic libraries with a cross-species cDNA probe. This is supported by the signed declaration under 37 C.F.R. 1.132 signed by Dr. Krieger and Dr. Acton. One of skill in the art would be able to use the teachings of the present specification to derive, and thus be in possession of, a human SR-BI. The legal standard for written description is met.

Rejection Under 35 U.S.C. § 112, second paragraph

Claims 11-13 and 19-22 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. Applicants respectfully traverse this rejection.

The Legal Standard

The legal standard for definiteness states that "definiteness of claim language must be analyzed, not in a vacuum, but in light of:

A) The content of the particular application disclosure

B) The teachings of the prior art

C) The claim interpretation that would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was made.

In reviewing a claim for compliance with 35 U.S.C. 112, second paragraph, the examiner must consider the claim as a whole to determine whether the claim apprises one of ordinary skill in the art of its scope and therefore, serves the notice function required by 35 U.S.C. 112, second paragraph. See, e.g. Solomon v Kimberly-Clark Corp., 216 F.3d 1372, 1379, 55 USPQ2d 1279, 1283 (Fed.Cir. 2000) (MPEP 2173.02)

The patentable subject matter should be defined with a "reasonable degree of particularity and distinctness". "Some latitude in the manner of expression and the aptness of terms should be permitted even though the claim language is not as precise as the Examiner might desire." (MPEP 2173.02)

The term "scavenger receptor protein type B1" is definite

This term is defined by other limitations in the claim such as ligand binding affinity, and hybridization conditions. These limitations define the SR-BI described in the claim preamble and are also supported by definitions provided by the specification.

The property or properties that define this limitation are found in the specification from page 10, line 32 to page 12, line 2. This passage defines the properties of a scavenger receptor protein type BI alone and in relation to CD36, a member of the family to which SR-BI belongs. The SR-BI is defined as a scavenger receptor of the CD36 family wherein its binding of AcLDL is inhibited by native LDL. The SR-BI is most abundantly expressed in fat and is present in moderate levels in lung and liver. SR-BI displays a high affinity binding for acetylated LDL with an apparent dissociation constant in the range of approximately 5 μg protein/ml. More importantly, it is defined by structure as being complementary to the disclosed cDNA. This term is clearly defined by the specification such that one of skill in the art would understand its usage in the claims. The legal standard is met.

The term "under moderately stringent hybridization conditions" is definite

The claim limitation "under moderately stringent hybridization conditions at a temperature of approximately 25°C below the melting temperature of a perfectly based-paired double-stranded DNA" is definite. Moderately stringent hybridization conditions are defined in the specification on page 40 , lines 24-31. One of skill in the art would understand precisely what this limitation means. The melting temperature of a perfectly based-paired double-stranded DNA is similarly definite as one of skill in the art would easily be able to calculate the melting temperature, and therefore discern the "moderately stringent hybridization conditions".

The Examiner is reminded that "Breadth of a claim is not to be equated with indefiniteness. "In re Miller, 441 F.2d 689, 169 USPQ 597 (CCPA 1971). The scope of the subject matter embraced by the claims is clear. The legal standard is met.

Rejection Under 35 U.S.C. § 102 and § 103

Claims 11, 19 and 20 were rejected under 35 U.S.C. § 102(a) and 35 U.S.C. § 103(a) as being anticipated and unpatentable by Calvo et al., J. Biol Chem, (1993), 268(25): 18929-18935 ("Calvo"). Applicants respectfully traverse this rejection.

The Legal Standard

For a rejection of claims to be properly founded under 35 U.S.C. § 102, it must be established that a prior art reference discloses each and every element of the claims. *Hybritech Inc v Monoclonal Antibodies Inc*, 231 USPQ 81 (Fed. Cir. 1986), *cert. denied*, 480 US 947 (1987); *Scripps Clinic & Research Found v Genentech Inc*, 18 USPQ2d 1001 (Fed. Cir. 1991). The Federal Circuit held in *Scripps*, 18 USPQ2d at 1010:

Invalidity for anticipation requires that all of the elements and limitations of the claim are found within a single prior art reference. . . *There must be no difference* between the claimed invention and the reference disclosure, as viewed by a person of ordinary skill in the field of the invention. (Emphasis added)

A reference that fails to disclose even one limitation will not be found to anticipate, even if the missing limitation could be discoverable through further experimentation. As the Federal Circuit held in *Scripps, Id.*:

[A] finding of anticipation requires that all aspects of the claimed invention were already described in a single reference: a finding that is not supportable if it is necessary to prove facts beyond those disclosed in the reference in order to meet the claim limitations. The role of extrinsic evidence is to educate the decision-maker to what the reference meant to persons of ordinary skill in the field of the invention, not to fill in the gaps in the reference.

For a prior art reference to anticipate a claim, it must enable a person skilled in the art to practice the invention. The Federal Circuit held that "a §102(b) reference must sufficiently describe the claimed invention to have placed the public in possession of it. . . [E]ven if the claimed invention is disclosed in a printed publication, that disclosure will not suffice as prior art if it was not enabling." *Paperless Accounting Inc v Bay Area Rapid Transit Sys.*, 231 USPQ 649, 653 (Fed. Cir. 1986) (citations omitted).

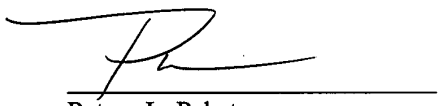
Calvo

Calvo reports the isolation of a cDNA encoding a member of the CD36 superfamily. The protein was not physically isolated nor was the cloned DNA expressed, much less expressed on the surface of cells and shown to be functional, although a small non-functional portion (corresponding to the carboxy-terminal residues 365-409) was expressed as a fusion protein. The function of the protein was not known, although its resemblance to CD36/LIMPII was recognized based on the predicted similarities in structure and the authors speculated that "on the basis of its structural homology to CD36 that CLA-1 could act as a receptor for extracellular products" (page 18934).

Claim 11 has been amended to include the claim limitation "encoding a functional scavenger receptor protein type BI" to distinguish this nucleic acid molecule over that of Calvo. Calvo did not express the full length *functionally* active protein, and therefore could not determine the utility of the protein. Calvo also does note teach a nucleic acid molecule encoding an *isolated* SR-BI. Further, the claim limitations also include the functional property that the SR-BI selectively binds to LDL and to AcLDL which are not disclosed in Calvo and would require further experimentation to show. Each and every limitation of these claims has not been disclosed in Calvo, and thus the legal standards for obviousness and anticipation have not been met.

Allowance of claims 11-15, 19-22, and 44-50 is respectfully solicited.

Respectfully submitted,



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Certificate of Mailing Under 37 C.F.R. § 1.8(a)

I hereby certify that this paper, along with any paper referred to as being attached or enclosed, is being deposited with the United States Postal Service on the date shown below with sufficient postage as first-class mail in an envelope addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231.

Aisha Wyatt

Date: February 10, 2000

Marked up Version of Amended Claims
Pursuant to 37 C.F.R. § 1.121(c)(1)(iii)

11. (three times amended) An isolated nucleic acid molecule encoding a functional scavenger receptor protein type BI which selectively binds to low density lipoprotein and to modified lipoprotein having the characteristics of acetylated low density lipoprotein in cell medium containing 10% serum, which hybridizes to SEQ ID Nos. 3 and 7 under moderately stringent hybridization conditions at a temperature of approximately 25°C below the melting temperature of a perfectly base-paired double-stranded DNA.

12. (amended) The molecule of claim 11 expressed in cells selected from the group consisting of adipocytes, lung cells and liver cells.

13. (twice amended) The molecule of claim 11 hybridizing under stringent hybridization conditions at a temperature greater than 25°C below the melting temperature of a perfectly base-paired double-stranded DNA to a molecule with Sequence ID No. 3.

14. (twice amended) An isolated nucleic acid molecule encoding a scavenger receptor protein having the sequence of Sequence ID No. 3.

15. (twice amended) An isolated nucleic acid molecule encoding a protein with the amino acid sequence shown in Sequence ID No. 4.

19. (twice amended) The molecule of claim 11 which encodes a human scavenger receptor.

20. (amended) The molecule of claim 11 labeled with a detectable label.

21. (three times amended) An expression vector comprising the molecule of claim 11 encoding the scavenger receptor protein.

22. (three times amended) A host cell comprising the nucleic acid molecule of claim 11.

44. (twice amended) A method for screening for a compound which alters the binding of scavenger receptor protein type BI, which is encoded by a nucleotide molecule hybridizing to SEQ ID Nos. 3 and 7 under moderately stringent hybridization conditions at a temperature of approximately 25°C below the melting temperature of a perfectly base-paired double-stranded DNA and which selectively binds to low density lipoprotein and to modified lipoprotein having the characteristics of acetylated low density lipoprotein in cell medium containing 10% serum, comprising

providing reagents for use in an assay for binding of low density lipoprotein or modified low density lipoprotein to the scavenger receptor protein the reagents comprising SR-BI, low density lipoprotein or modified low density lipoprotein, and means for determining if the low density lipoprotein or modified low density lipoprotein is bound to the scavenger receptor protein,

adding the compound to be tested to the assay, and

determining if the amount of modified low density lipoprotein or low density lipoprotein which is bound to the scavenger receptor protein is altered as compared to binding in the absence of the compound to be tested.

45. (amended) The method of claim 44 wherein the assay includes a cell expressing the scavenger receptor protein and the compound is a nucleic acid molecule which alters expression of the scavenger receptor protein.

46. (amended) The method of claim 44 wherein the compound is selected from a library of compounds which are randomly tested for alteration of binding.

47. (amended) The method of claim 44 wherein the compound competitively inhibits binding of low density lipoprotein or modified lipoprotein having the characteristics of acetylated low density lipoprotein to the scavenger receptor protein.

48. (twice amended) A method for removing low density lipoprotein from patient blood comprising reacting the blood with immobilized scavenger receptor protein type B, wherein the scavenger receptor protein type BI is encoded by a nucleotide molecule hybridizing to SEQ ID Nos. 3 and 7 under moderately stringent hybridization conditions at a temperature of approximately 25°C below the melting temperature of a perfectly base-paired double-stranded DNA and selectively binds to low density lipoprotein and to modified lipoprotein having the characteristics of acetylated low density lipoprotein in cell medium containing 10% serum, under conditions wherein the low density lipoprotein is bound to the scavenger receptor.

49. (twice amended) A method for inhibiting uptake of lipoprotein or lipids by adipocytes comprising

administering a compound selectively inhibiting binding of lipoprotein to the scavenger receptor protein type BI, wherein the scavenger receptor protein type BI is encoded by a nucleotide molecule hybridizing to SEQ ID Nos. 3 and 7 and selectively binds to low density

lipoprotein and to modified lipoprotein having the characteristics of acetylated low density lipoprotein, under conditions wherein the low density lipoprotein is bound to the scavenger receptor.

50. (amended) A method for screening patients for abnormal scavenger receptor protein activity or function comprising

determining the presence of scavenger receptor protein type BI, wherein the scavenger receptor protein type BI is encoded by a nucleotide molecule hybridizing to SEQ ID Nos. 3 and 7 under moderately stringent hybridization conditions at a temperature of approximately 25°C below the melting temperature of a perfectly base-paired double-stranded DNA and selectively binds to low density lipoprotein and to modified lipoprotein having the characteristics of acetylated low density lipoprotein, and

determining if the quantity present or the function of the receptor is equivalent to that present in normal cells.